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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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STEPHANIE L. SEIDMAN, ESQ.
HELLER EHRMAN WHITE & MCAULIFFE LLP
4350 LA JOLLA VILLAGE DRIVE
SUITE 600
SAN DIEGO CA 92122-1246

EXAMINER	
ZITOMER, S	
ART UNIT	**PAPER NUMBER**
1655	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

PTO-90C (Rev. 2/95)
*U S GPO: 2000-473-000/44602

Office Action Summary	Application No. 09/601,645	Applicant(s) DAHM
	Examiner S. ZITOMER	Art Unit 1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 6, 2001*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-68* is/are pending in the application.

4a) Of the above, claim(s) *1-19, 35-61, 67, and 68* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *20-34 and 62-66* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Application status

1. Receipt of the election filed August 6, 2001 is acknowledged.

2. An error in the restriction set forth in paper no. 9, mailed July 3, 2001, has been noted. Claim 67 was included in group II whereas it clearly belongs in group I in being dependent from claim 1. Thus the corrected claim groups I and II contain claims 1-19, 35-38, 52-61 and 67 and claims 20-34 and 62-66, respectively.

Response to applicant's traversal

3. The traversal is on the ground(s) that applicant disagrees that the special inventive feature of the claims is the telomerase catalytic subunit mRNA stating that the claims of Invention I are directed to methods for quantification of tumor cells in a body fluid by concentrating the cells, amplifying the mRNA for the telomerase catalytic subunit and quantifying the mRNA while the Invention II claims depend from claim 1 and therefore are directed to the same invention. This is not found persuasive because none of the group I particulars of amplifying and quantifying mRNA are found in the group II claims and conversely, the group II methods for concentrating tumor cells from blood involving culture, centrifugation and cell separation medium are not found in the group I claims. Thus, the mRNA for telomerase catalytic subunit, which was known in the prior art, is the special technical feature of both claim groups. Regarding applicant's discussion of the Sidransky and Selby references, it is pointed out that these were cited as a courtesy to applicant to show that concentrating cells and amplifying and quantifying mRNA were known techniques in the art. The only reference required of the examiner was that disclosing the special technical feature. Applicant is reminded that the issue is restriction, not rejection over prior art. Finally, regarding the discussion of double patenting rejection being disallowed over claims in a different restriction group, it is pointed out that the "second patent" cited by applicant, i.e., claims of Invention II, would not be obvious over the claims of Invention I in any case because the concentration method of the latter is generic and the particulars of the former group would not be obvious over the generic method. Of course, if the claims in either Invention group were to be amended to include particulars from the other Invention, double patenting would then apply.

The requirement is still deemed proper and is therefore made FINAL.

Priority information

4. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Compliance with Sequence Rules

5. This application fails to comply with the Rules for Nucleotide Sequences (MPEP 8.21-8.25) for two reasons: there is no hard copy of the Sequence Listing in the application and the nucleotide sequences in the specification (e.g., pages 8 and 15) do not have SEQ ID NOS:. Appropriate correction is required.

Rejection under 35 U.S.C. 112, first paragraph: Lack of written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 20-34 and 62-66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are drawn to a method for "the quantification of tumor cells in a body fluid". However, the disclosure fails to describe how to quantify tumor cells. The specification describes methods for concentrating tumor cells spiked in blood, lysing the concentrated cells, extracting RNA, specifically amplifying mRNA for the catalytic subunit of telomerase and quantifying this mRNA by coamplification of a standard nucleotide sequence (pages 12-16 and Examples). No teaching of a correlation between the amount mRNA for the catalytic subunit of telomerase and tumor cells is provided. Therefore, the specification fails to describe how to perform the invention method as claimed. In addition to enablement the first paragraph of 112 requires a "written description". As set forth by the Court in *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, the written description must convey to one of skill in the art "with reasonable clarity" that as of the filing date applicant was in possession of the

claimed invention. Absent teaching of how to quantify tumor cells based on a quantity of mRNA for the catalytic subunit of telomerase the disclosure fails to provide a written description of the claimed invention method and fails to demonstrate that applicant was in possession of the claimed invention at the time the application was filed.

Rejections under 35 U.S.C. 112, second paragraph: Indefiniteness

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 20-34 and 62-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) The claims are indefinite in depending from a nonelected claim.

(b) The claims are incomplete in omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps: are lysing the concentrated cells and isolating their RNA prior to amplification. See page 6, lines 12-20, page 34 at 3. and page 39, lines 5-8.

(c) The claims are confusing at the recitation "for concentrating the tumor cells" because it is unclear due to the improper claim format whether this is a method step.

(d) The claims are further confusing because the method steps lack relationship with one another. For example, the source of the mRNA in step (b) is not stated.

(e) Claim 24 has confusing syntax because the subject referred by "it" is unclear at both occurrences.

(f) Claim 24 lacks proper antecedent basis in claim 20 because platelets are found in blood and claim 20 does not recite that the body fluid is blood.

(g) Clam 29 is confusing and lacks proper antecedent basis in claim 20 for the recitation "the tumor-cell-enriched interphase" because the phrase is not related to the subject matter of claim 20. The term "interphase" refers to a stage in the cell cycle.

(h) In claim 29, the term "intensively" is a relative term which renders the claim indefinite. The term "intensively" is not defined by the claim, the specification does not

provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

(l) Claim 34 is confusing in lacking proper antecedent basis and being in improper claim format because no step of adding a dye to the cell separation medium is recited.

(j) The claims are confusing because claim 1 which is incorporated in claim 20 has an improper "and" at the end of step (b).

Rejection under 35 U.S.C. 103(a): Obviousness

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 20-34 and 62-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selby (GB2,260,811) in view of Nakamura et al. (Science, 15 August 1997, 277:955-959 and further in view of Van Vlasselaer (5,648,223). Regarding claim 20, Selby discloses a method for the quantification of tumor cells in a body fluid comprising (a) concentrating the tumor cells in a sample of the body fluid; (b) specifically amplifying a mRNA; (c) quantitatively determining the amount of amplified nucleic acid thereby detecting tumor cells in a body fluid (page 10, last paragraph-page 11). The claimed invention method differs from that of Selby wherein the amplified mRNA is the mRNA for the catalytic subunit of telomerase and the tumor cells are quantified. However, Nakamura et al. teach amplification of the mRNA for the catalytic subunit of telomerase and quantification of the specific mRNA in telomerase-positive and telomerase-negative tumor cells (page 957, middle column). Accordingly, it would have been obvious at the time the claimed invention was made and the skilled practitioner in the art would have been motivated to amplify the mRNA for the catalytic subunit of telomerase as taught by Nakamura et al. in the method of Selby et al. in view of the teaching of Nakamura et al. that telomerase activity, which was known to be increased in cancer cells (page 955, lines 10-17 and page 957, middle column) correlates more strongly with the mRNA for the catalytic subunit of telomerase than with

telomerase RNA (page 957, middle column). It would have been further obvious to quantify the tumor cells by quantifying the mRNA for the catalytic subunit of telomerase in a test sample of the cells and comparing the ratio with that in the samples to be diagnosed as practiced in the art. Regarding claim 23, Percoll and Ficoll were routinely used in the art as cell separation media, for example, as taught by Van Vlasselaer in a method for concentrating tumor cells (column 4, line 60-column 5, line 5). It would have been obvious and the skilled practitioner in the art at the time the claimed invention was made would have been motivated to employ a cell separation medium that was proven in the art and readily available for the obvious benefits thereof. Regarding claims 25-28, Selby teaches that the body fluid is peripheral blood (page 4, last paragraph) (obviously venous or arterial which are the two types of blood vessels) and Van Vlassalaer teaches that the body fluid is lymph or blood or the like (column 2, lines 30-33). Regarding claims 21, 22, 24 and 62-64, it would have been obvious to the skilled practitioner in the art to adjust the density of the cell separation medium and centrifugation speed according to the type of tumor cell to be concentrated. For example, Van Vlassalaer teaches that the medium density is adjusted to the density of the cell type (column 9, lines 47-66; column 14, Example 6.1.1 and 6.1.2) and that for breast tumor cells, the specific density was adjusted within 0.0005 g/ml of the specific density of the tumor cells and the centrifugation speed is at a gravitational force sufficient to pellet the cells (column 16, lines 61-67). It would have been further obvious to provide a substance that prevents platelets from sticking to the tumor cells and to remove the platelets as routinely practiced in the art. Regarding claim 29, cooling after centrifugation was routinely practiced in the art, for example, as taught by Selby (page 10, last paragraph). Regarding claims 30-34 and 65-67, Van Vlassalaer teaches that centrifugation is carried out in a tube divided by a barrier (column 5, lines 30-54) wherein the barrier is an annular ring. However, it would have been obvious to one of ordinary skill in the art to use a barrier comprised of porous material , filter or sieve as routinely practiced in conventional differential centrifugation wherein the material and the thickness and pore size thereof as well as the degree of dilution of the medium would have been selected according to experimental requirements. It would have been further obvious to employ a colored separation medium for ease of layer recognition as routinely practiced in the art.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephanie Zitomer whose telephone number is (703) 308-3985. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152. The official fax phone number for this Group is (703) 308-4242. The unofficial fax number is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

S Zitomer

Stephanie Zitomer, Ph.D.

October 22, 2001